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Diagnostic radiation and the risk of multiple myeloma (United States)

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Abstract

Objective: To evaluate the relationship between cumulative lifetime exposure to diagnostic radiation and the risk of multiple myeloma using data from a large, multi-center, population-based case–control study.
Methods: Study subjects included a total of 540 cases with newly diagnosed multiple myeloma and 1998 frequency-matched population controls living in three areas of the United States (Georgia, Michigan, New Jersey). Information on exposure to diagnostic X-rays was obtained by personal interview.
Results: No association was found between case–control status and the total number of reported diagnostic X-rays of any type (odds ratio (OR) for 20 or more compared to less than 5 X-rays = 0.9, 95% confidence interval (95% CI) = 0.7–1.2). There was no evidence of an excess risk of multiple myeloma among individuals who reported exposure to 10 or more diagnostic X-rays that impart a relatively high radiation dose to the bone marrow, as compared to individuals reporting no such exposures (OR 0.7, 95% CI 0.4–1.3).
Conclusions: These data suggest that exposure to diagnostic X-rays has a negligible impact, if any, on risk of developing multiple myeloma.

Introduction

Multiple myeloma is a hematopoietic malignancy in which an excess number of plasma cells collect in the bone marrow and produce elevated levels of an immunoglobulin [1], commonly IgG or IgA [2]. This disorder accounts for more than 1% of all cancer cases and nearly 2% of cancer-related deaths in the United States [3]. The incidence of multiple myeloma increases with age, is greater among men than among women, and is higher among blacks than among whites in the United States [1, 3–6]. Although certain occupational exposures, autoimmune diseases, and genetic factors have been suggested as risk factors, the etiology of multiple myeloma is not well understood.

The present study investigated the relationship between multiple myeloma and the low levels of ionizing radiation from diagnostic X-rays. Prior research examining the relationship between radiological examination and risk of multiple myeloma has yielded inconsistent results. Four studies have reported an increased risk of multiple myeloma associated with diagnostic radiation [2, 7–9], while five others found no such relationship [10–14]. A number of these studies were limited by relatively modest sample sizes. To address this limitation we analyzed data from the largest case–control study to date to investigate the relationship between diagnostic radiation and multiple myeloma.

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Materials and methods

This study was one component of a multi-center, population-based case–control study of multiple myeloma and cancers of the esophagus, pancreas, and prostate, all of which have a higher incidence among blacks than among whites. Study participants were residents of geographic areas covered by three population-based cancer registries: the Georgia Center for Cancer Statistics, the Metropolitan Detroit Cancer Surveillance System, and the New Jersey State Cancer Registry.

Eligible cases were white residents and black residents aged 30–79 years, newly diagnosed with multiple myeloma between 1 August, 1986 and 30 April, 1989. Cases were identified from pathology, hematology, outpatient, and tumor registry records at hospitals in the three areas. To mitigate non-participation due to the rapid progression of multiple myeloma, a rapid ascertainment system was employed to identify and interview patients within 3 months of diagnosis. In practice nearly all cases were interviewed within 6 months. Of the 581 white and 309 black eligible cases ascertained, interviews were successfully conducted with 367 whites (63%) and 208 blacks (67%). Reasons for non-response included death (21% for both races), illness (whites 7%, blacks 6%), and patient or physician refusal (whites 9%, blacks 5%).

For efficiency a single control group was recruited for all four case types in the parent study. Controls were frequency-matched to the expected distributions, based on registry data from prior years, of age (5-year age groups), race, gender, and registry area for all four cancer types combined. Random-digit dialing (RDD) was employed to select controls aged 30–64 years. Controls aged 65–79 were identified through random sampling from computerized listings of Medicare recipients, provided by the Health Care Financing Administration (HCFA) and stratified by age, race, and gender for each registry area. The overall participation rate, accounting for response at initial screening and at interview, was 67% among both blacks and whites for RDD controls. Additionally, the participation rate was 73% for whites and 78% for blacks for the HCFA controls, yielding a total of 2153 successful control interviews. Reasons for non-response included refusal (whites 17%, blacks 13%), illness or death (whites 3%, blacks 4%), and other problems (whites 3%, blacks 4%).

Cases and controls were interviewed in person by trained interviewers, generally in the subject's home. The questionnaire requested detailed information on sociodemographic factors, medical history, alcohol and tobacco use, diet, and lifetime occupational history. Participants were asked to report how many different times, "before 1 year ago," they had diagnostic X-rays of the following types: chest fluoroscopy, regular chest X-ray, upper gastrointestinal tract (GI), cholangiogram, lower GI, angiogram, intravenous pyelogram (IVP), thyroid scan, and venogram or arteriogram. Female subjects were asked also to report numbers of mammograms and pelvic X-rays. Respondents were allowed to report up to a maximum of 95 exposures to any given X-ray type. Participants were also asked to report how many different times, "not counting the past year," they had diagnostic X-rays for any type of injury, lower back problem, or other pains in a muscle or joint. Subjects were asked to respond using the following categories: 0 times, 1–4 times, 5–9 times, 10–19 times, and 20 or more times. Finally, participants were asked to report the number of dental X-ray sessions they had during their adult life only, not counting the past year. This response was queried in the following categories: 0 sessions, 1–4 sessions, 5–9 sessions, 10–24 sessions, and 25 or more sessions.

Cumulative lifetime exposure to diagnostic X-rays was derived in two different ways. First, a value for the cumulative lifetime number of diagnostic X-rays of all types combined was created by summing the reported number of X-ray exposures of each X-ray type and the midpoint value (0, 2.5, 7, 14.5, or 24.5) for the categories representing the number of diagnostic X-rays for any type of injury, lower back problem, or other pains in a muscle or joint. Individuals with a missing value for any of the X-ray types involved in the summation were assigned a missing value for the sum. Sensitivity analyses were conducted to evaluate the impact of inclusion of the midpoint value (0, 2.5, 7, 17, or 32) of number of dental X-rays during adulthood. Second, each X-ray type was categorized according to its relative dose to the bone marrow (highest, medium, or lowest), based on a review of published estimated doses to the bone marrow for each X-ray type [15–20], with Kereiakes and Rosenstein [19] and Shleien *et al.* [17] serving as the primary sources. Summation of the cumulative lifetime number of relative high-, medium-, and low-dose X-rays was carried out as above. Sensitivity analyses were conducted to evaluate the impact of inclusion of dental X-rays in the lowest dose category, and of diagnostic X-rays for "any type of injury, lower back problem, or other pains in a muscle or joint" in each category, in turn.

Individuals who reported prior exposure to radiation treatment for any disorder were excluded from the present analyses (6% of interviewed cases, 7% of interviewed controls). Also excluded were 15 white controls aged 30–34 years, because there were no

comparably aged white cases, and two cases and seven controls with unreliable responses as assessed by the interviewer. Analyses were conducted using 540 cases and 1998 controls.

Following stratified analyses to evaluate which potential confounders and effect measure modifiers to include in the modeling process, unconditional logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) using the SAS logistic procedure [21]. ORs were adjusted for education (less than high school, high school or equivalent, more than high school) and for the matching factors: age (30–34, 35–39, . . ., 75–79), race (black, white), gender (male, female), and geographic area (Atlanta, Detroit, New Jersey). All variables were specified as indicator variables. Potential effect measure modification, on the multiplicative scale, was evaluated initially via stratified analyses using the test of homogeneity, and subsequently in the full logistic model using likelihood ratio tests and examination of stratum-specific ORs. Age, race, gender, and education were considered as potential effect measure modifiers. Additionally, analyses were carried out separately for multiple myeloma cases of the two major immunoglobulin subtypes, IgG and IgA, as determined by abstraction from medical records. Of the 540 cases used in the present analyses, information regarding immunoglobulin subtype was available for 390 individuals, 229 of whom were of the IgG subtype and 97 of whom were of the IgA subtype.

Table 1. Distribution of cases and controls by sociodemographic factors

	Cases (n = 540)		Controls (n = 1998)	
	No.	Percentage	No.	Percentage
Study site[a]				
Atlanta	62	11.5	409	20.5
Detroit	237	43.9	810	40.5
New Jersey	241	44.6	779	39.0
Age (years)[a]				
30–39	11	2.0	47	2.4
40–49	40	7.4	239	12.0
50–59	107	19.8	538	26.9
60–69	201	37.2	611	30.6
70+	181	33.5	563	28.2
Race[a]				
Black	202	37.4	927	46.4
White	338	62.6	1071	53.6
Gender[a]				
Male	269	49.8	1279	64.0
Female	271	50.2	719	36.0
Education				
Some college	127	23.5	596	29.8
High school	158	29.3	579	29.0
0–11 years	253	46.9	814	40.7
Missing	2	0.4	9	0.5

[a] Matching factor.

Results

Table 1 presents the distribution of matching and selected demographic factors among cases and controls. The average age was 64 years for cases and 62 years for controls. As found in a prior analysis of these data [22], cases tended to have less education than controls. The distribution of some, but not all, of the matching factors was similar among cases and controls. The discrepancies likely are due to the matching of controls to all four cancer case types combined. All matching factors were adjusted for in all analyses.

The distribution of exposure to diagnostic X-rays, classified by type and relative dose category, among cases and controls is shown in Table 2. Some individuals reported a very large number of procedures, but a sensitivity analysis did not show any meaningful influence on the main results. The most common X-ray exposures were chest X-rays, dental X-rays, and diagnostic X-rays for any type of injury, lower back problem, or other pains in a muscle or joint. There were no striking patterns of difference between cases and controls. Cases and controls reported similar levels of past exposure to X-rays that deliver a high or medium relative dose to the bone marrow. Slightly more controls (85%) than cases (80%) reported a history of exposure to X-rays that deliver the lowest doses to the bone marrow, including X-rays and photofluorographs of the chest, and mammograms among females. Controls were also slightly more likely than cases to report exposure to X-rays to check for any type of injury, lower back problem, or other pains in a muscle or joint (controls 64%, cases 59%), and to report having undergone any type of diagnostic X-ray, excluding dental examinations (controls 88%, cases 83%). The proportion of cases and controls with missing values for each X-ray type ranged from less than 1% to just over 7% for individual exposures other than dental X-rays.

On average, white controls reported exposure to a slightly greater total number of diagnostic X-rays of any type, excluding dental X-rays, than did black controls (18.0 *versus* 15.2 average total number of X-rays of any type), and controls with education past high school had a somewhat higher mean reported number of diagnostic X-rays than did controls with a high-school education or less (19.9 *versus* 15.3 average total number of X-rays; data not shown). Reported total number of X-rays,

Table 2. Number of cases and controls ever exposed to specific radiographic examinations and mean, median, and maximum number of examinations per exposed individual

Diagnostic examination	Cases (n = 540)			Controls (n = 1998)		
	No. exposed (% of cases)	No. missing (% of cases)	Examinations per exposed person mean, median (max)	No. exposed (% of controls)	No. missing (% of controls)	Examinations per exposed person mean, median (max)
Highest dose X-rays						
Pelvis (females only)	39 (14.4%)[a]	14 (5.2%)[a]	1.9, 1.0 (12.0)	139 (19.3%)[a]	21 (2.9%)[a]	2.1, 1.0 (20.0)
Upper GI (stomach)	267 (49.4%)	7 (1.3%)	2.2, 1.0 (26.0)	965 (48.3%)	15 (0.8%)	2.3, 1.0 (31.0)
Lower GI/barium enema	191 (35.4%)	8 (1.5%)	2.2, 1.0 (26.0)	733 (36.7%)	14 (0.7%)	2.1, 1.0 (95.0)[b]
IVP (kidney)	79 (14.6%)	30 (5.6%)	1.7, 1.0 (10.0)	299 (15.0%)	120 (6.0%)	2.0, 1.0 (35.0)
Any high-dose X-ray[c]	288 (53.3%)	35 (6.5%)	3.9, 2.0 (52.0)	1088 (54.5%)	131 (6.6%)	4.0, 2.0 (117.0)
Medium-dose X-rays						
Cholangiogram (gallblader)	105 (19.4%)	6 (1.1%)	1.5, 1.0 (5.0)	342 (17.1%)	14 (0.7%)	1.6, 1.0 (20.0)
Angiogram (heart)	55 (10.2%)	28 (5.2%)	1.5, 1.0 (6.0)	238 (11.9%)	124 (6.2%)	2.2, 1.0 (70.0)
Any medium-dose X-ray[c]	132 (24.4%)	30 (5.6%)	1.8, 1.0 (10.0)	496 (24.8%)	127 (6.4%)	2.1, 1.0 (71.0)
Lowest-dose X-rays						
Fluoroscopy (chest)	48 (8.9%)	35 (6.5%)	6.8, 2.0 (95.0)[b]	242 (12.1%)	136 (6.8%)	5.3, 2.0 (95.0)[b]
Chest (regular)	434 (80.4%)	40 (7.4%)	9.7, 6.0 (95.0)[b]	1683 (84.2%)	148 (7.4%)	9.6, 6.0 (95.0)[b]
Mammogram (females only)	106 (39.1%)[a]	14 (5.2%)[a]	2.7, 1.0 (17.0)	308 (42.8%)[a]	17 (2.4%)[a]	2.8, 2.0 (24.0)
Thyroid scan	25 (4.6%)	29 (5.4%)	1.5, 1.0 (4.0)	98 (4.9%)	124 (6.2%)	2.2, 1.0 (30.0)
Any low-dose X-ray[c,d]	434 (80.4%)	49 (9.1%)	10.8, 7.0 (109.0)	1693 (84.7%)	175 (8.8%)	10.7, 6.0 (148.0)
Variable-dose X-rays						
Venogram or arteriogram	26 (4.8%)	29 (5.4%)	1.4, 1.0 (4.0)	115 (5.8%)	132 (6.6%)	1.4, 1.0 (9.0)
Any of:						
Injury, lower back problems, other muscle/joint pains	318 (58.9%)	9 (1.7%)	7.1, 2.5 (24.5)[b]	1287 (64.4%)	39 (2.0%)	6.0, 2.5 (24.5)[b]
Any diagnostic X-ray exposure[c,d]	447 (82.8%)	58 (10.7%)	17.4, 12.5 (124.5)	1748 (87.5%)	198 (9.9%)	17.2, 12.0 (250.5)
Dental (adult exposure only)	432 (80.0%)	45 (8.3%)	12.2, 7.0 (32.0)[b]	1615 (80.8%)	184 (9.2%)	11.7, 7.0 (32.0)[b]

[a] Percentage of female cases (n = 271) or controls (n = 719).
[b] Maximum value determined by variable specification or derivation.
[c] Considered missing if missing for any X-ray type.
[d] Does not include dental X-ray exposures.

excluding dental examinations, tended to increase slightly with age, but did not differ notably by sex (data not shown). All of these trends were driven by the distribution of the lowest dose X-rays.

Table 3 presents the adjusted ORs for cumulative lifetime number of diagnostic X-rays of any type, excluding dental examinations. No elevated risk of multiple myeloma was detected for lifetime exposure to five or more diagnostic X-rays as compared with lifetime exposure to fewer than five diagnostic X-rays, and there was no positive gradient in risk with increasing number of X-ray exposures. For example, the OR for 20 or more X-rays compared to less than five X-rays was 0.9 (CI 0.7–1.2). Inclusion of dental X-rays did not notably alter these results. The OR for 20 or more X-rays compared to less than five X-rays was 0.8 (CI 0.5–1.2) upon inclusion of dental X-ray information. There was no meaningful effect measure modification by race, gender, age, or level of education (data not shown). Separate analyses by immunoglobulin subtype revealed no important differences between the case subtypes. The effect of 20 or more X-rays compared to less than five X-rays was 1.0 (CI 0.6–1.5) among the 204 IgG cases with complete exposure data and 0.8 (CI 0.4–1.4) among the 83 IgA cases with complete exposure data.

The results of the analysis of cumulative lifetime numbers of diagnostic X-rays with relative high, medium, and low doses to the bone marrow are presented in

Table 3. Odds ratios (ORs) and 95% confidence intervals (95% CI) for multiple myeloma by cumulative lifetime number of diagnostic X-rays

Total number of diagnostic X-rays	Cases	Controls	OR (95% CI)[a]
0–<5	106	371	1.0 (ref)
5–<10	104	396	0.9 (0.7–1.2)
10–<20	133	483	1.0 (0.7–1.3)
20+	137	543	0.9 (0.7–1.2)
Missing[b]	60	205	

[a] ORs are adjusted for education and for matching factors: age, race, gender, and state of residence.
[b] Number of individuals with missing values for total number of diagnostic X-rays or education.

Table 4. Odds ratios (ORs) and 95% confidence intervals (95% CI) for multiple myeloma by cumulative lifetime number of relative high-, medium-, and low-dose diagnostic X-rays

	Cases	Controls	OR (95% CI)[a]
Highest-dose X-rays			
0	210	759	1.0 (ref)
1–<5	217	787	0.9 (0.7–1.2)
5–<10	39	182	0.8 (0.5–1.1)
10+	17	75	0.7 (0.4–1.3)
Medium-dose X-rays			
0	361	1330	1.0 (ref)
1–<3	104	394	0.9 (0.7–1.1)
3+	18	79	0.8 (0.4–1.3)
Lowest-dose X-rays			
0	57	128	1.0 (ref)
1–<5	140	592	0.5 (0.4–0.8)
5–<10	98	393	0.6 (0.4–0.9)
10+	188	690	0.7 (0.5–1.0)
Missing[b]	57	195	

[a] ORs are adjusted for education and for matching factors: age, race, gender, and state of residence.
[b] Number of individuals with missing values for any X-ray dose category or education.

Table 4. The specific X-ray types that define each category are as shown in Table 2. All ORs are adjusted for matching factors and education. Exposure to X-rays in the highest-dose category was not associated with an elevated risk of multiple myeloma (Table 4). The OR for 10 or more highest-dose X-rays relative to zero highest-dose X-rays was 0.7 (CI 0.4–1.3). Likewise, no elevated risk was detected among individuals exposed to medium-dose X-rays. The OR for three or more medium-dose X-rays *versus* none was 0.8 (CI 0.4–1.3). The data suggest a possible decreased risk of multiple myeloma associated with ever having any lowest-dose X-rays (OR, 1–<5 lowest dose X-rays versus none = 0.5, CI 0.4–0.8), although there is no evidence of a monotonic dose–response trend (p-trend = 0.8). Inclusion of dental X-rays in the lowest-dose category diminished this suggested relationship (OR, 1–<5 lowest-dose X-rays *versus* none = 0.9, CI 0.4–2.3), because this highly prevalent exposure showed no association with multiple myeloma risk (OR, 25 or more dental X-rays *versus* none = 0.9, CI 0.5–1.3; data not shown). Sensitivity analyses of the inclusion of number of diagnostic X-rays for any type of injury, lower back problem, or other pains in a muscle or joint were conducted. Inclusion of this variable-dose exposure in each relative dose category, in turn, led to negligible changes in estimated ORs (data not shown). There was no notable effect measure modification by race in the medium- or lowest-dose categories. Although stratification by race suggested a greatly decreased risk associated with exposure to 10 or more relatively high-dose X-rays among blacks, and no such decreased risk among whites, the estimate among blacks was quite imprecise and based on only two exposed cases. There were no other important differences in effect measures according to gender, age, level of education, or immunoglobulin subtype for any relative dose category (data not shown). The OR estimates for each relative dose category (highest, medium, lowest) were not materially altered upon further adjustment for the number of X-rays in the other two dose categories.

Discussion

This population-based, case–control interview study found no evidence of excess risk of multiple myeloma associated with cumulative lifetime exposure to diagnostic X-rays, whether analyzed in aggregate or separately by relative dose to the bone marrow. These results did not vary with race, gender, age, education, or immunoglobulin subtype.

Our findings are in agreement with several previous epidemiologic studies that have reported no association between exposure to diagnostic X-rays and risk of multiple myeloma. These include three questionnaire-based case–control studies [11, 13, 14] and one utilizing medical records [10], as well as a cohort mortality study of tuberculosis patients exposed to X-ray fluoroscopy as recorded in medical records [12]. Although one of these studies [14] evaluated X-ray exposure to a few specific parts of the body, none explicitly incorporated information on specific or relative dose to the bone marrow when estimating multiple myeloma risk.

A handful of studies have found positive associations between diagnostic X-ray exposure and multiple

myeloma. In a study of 208 cases and 262 controls within two prepaid health plans, Boice and colleagues [8] reported a three- to four-fold increased risk of multiple myeloma among those individuals exposed to the highest category of estimated cumulative bone-marrow dose, due to diagnostic radiation, as compared with those in the lowest category. Diagnostic X-ray history was abstracted from medical records. Flodin *et al.* [9] conducted a population-based case–control study, based on a mailed questionnaire, and reported an elevated but very imprecise OR for individuals exposed to high-dose X-rays (OR 2.9, CI 0.4–19.4; 2 exposed cases). Unlike the present study, and a number of other studies reporting no association between multiple myeloma and diagnostic radiation, these two studies did not analyze lifetime exposure data. Boice *et al.* [8] only had exposure information spanning between 5 and 25 years, and Flodin *et al.* [9] assayed exposures only for the period between 10 and 30 years prior to diagnosis. At the same time Boice, *et al.* were able to incorporate information on the distribution of X-ray exposures over time; whereas we were unable to do so because the timing of each X-ray exposure was not ascertained in the interview. However, this is unlikely to account for the discrepancy in the findings, as Boice and colleagues found similar dose–response results irrespective of lag time. A third positive, population-based, case–control study [2] found a moderately elevated risk of multiple myeloma associated with having one or more self-reported chest X-rays per year as compared with having fewer than one chest X-ray every 5 years (OR 1.6, CI 0.9–2.8). This relationship was detected among individuals with IgA myeloma, but not among individuals with IgG myeloma. A similar IgA-specific relationship was found for dental X-rays (OR 1.6, CI 0.9–3.1). Although the present study did not detect any effect specific to immunoglobulin subtype, some of the effect estimates were quite imprecise.

The present study is, to our knowledge, the largest case–control study to date investigating the relationship between diagnostic radiation and multiple myeloma. Additional strengths of our study include its population-based design, use of incident cases, and analysis of the sensitivity of our results to variations in exposure definition.

Limitations of our study include relatively low response, lack of information on the timing of individual exposures, and reliance on self-report. In addition, as evidenced by the wide confidence interval associated with the OR for the highest-dose category (10+), the study had limited power to detect small effects at the highest estimated exposure to low-dose radiation.

Two validation studies have compared reporting of exposure to diagnostic X-rays, via interview, with medical record information. These studies, however, are not directly applicable to the present study because one relied largely on proxy respondents to provide answers to the questionnaire [23], and the other employed a highly specific, probing questionnaire and assayed only dental X-ray exposure history [24]. It is noteworthy, however, that this latter study did not find any difference in reporting by case–control status. If non-differential, recall error would tend to bias our results toward the null, under most conditions [25, 26].

It is possible that any effect on cancer risk of the protracted low doses of radiation associated with diagnostic X-rays may be too small to detect using epidemiologic methods [27, 28]. Based on data from Kereiakes and Rosenstein [19], the average dose to the bone marrow due to individual X-ray exposures in our study likely ranged from approximately 0.00004 Gray (Gy) for a single low-dose chest X-ray to 0.003 Gy for a relatively higher-dose lower GI/barium enema. The available information did not allow for a reliable estimation of lifetime dose to study participants. However, an approximate estimation, excluding variable-dose X-rays, suggests that exposed participants in our study population reported lifetime X-ray exposures equivalent to roughly 0.00004–0.11 Gy of cumulative radiation exposure, with 99% of these subjects likely exposed to 0.03 Gy or less. Some authors have suggested that the relative risk associated with low radiation doses on the order of 0.01–0.10 Gy, a range compatible with the range of estimated lifetime doses in our study population, may be considerably less than 1.1 [28]. This value is plausible for multiple myeloma, given a range of relative risk estimates (RR = 1.0–3.3) associated with doses of 1 Gy in prior studies of multiple myeloma and high doses of radiation [28]. The true shape of the dose–response curve at low doses of ionizing radiation, however, is unknown [28, 29].

In summary, our study suggests that exposure to diagnostic X-rays has no discernible impact on the incidence of multiple myeloma. This finding is consistent with that of a recent literature review in the UNSCEAR 2000 Report, which concluded that there is little overall evidence of an association between multiple myeloma risk and low-intensity radiation [30]. Also noteworthy is the most recent analysis of multiple myeloma incidence among atomic bomb survivors, which indicated no increased risk associated with radiation exposure [31]. Further research is needed to elucidate the environmental and genetic determinants of multiple myeloma and reasons for its racial discrepancy in incidence. Emerging data on the possible genetic basis of multiple myeloma [32] may allow

for the eventual analysis of potential interactions between environmental exposures and genetic predisposition.

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